Annals of Oncology Editorial
Weighing false hope in population anti-cancer drug decision-making

The cost of anti-cancer pharmaceuticals is increasing.(1) While there are those that would argue the costs of anti-cancer drugs have escalated out of proportion to the benefit they provide(2) there are others who feel these costs are justified.(3) Despite numerous policy approaches to address the growing need for anti-cancer drugs (4, 5) there is no clear international consensus on what is fair when it comes to anti-cancer drugs access. The threshold of evidence required for anti-cancer drugs licensing may be less than in other disease types.(6, 7) This therefore has the potential to not only allow drugs with less evidence of benefit or harm to the market, but also may risk the generation of quality evidence about their outcome.(8) Morally and ethically, what responsibility do clinicians and policy makers have to define the context and level of uncertainty of evidence that is acceptable to allow patients access to 'try' anti-cancer drugs? And is there a concern about the cost- to an individual and to society of false hope?

In an area rife with disagreement about the fundamental costs and benefits of anti-cancer drugs to individuals and society Lipworth et al., present a conceptual framework to address this contentious area. Their framework summarizes 6 steps in the prioritisation of anti-cancer drugs debate:
Step 1: Define the clinical context (benefits, risks, alternatives, cost-effectiveness)
Step 2: Categorize the drug according to these findings (Type 1-3)

	Safe	Effective	Summary
Cost effective	✓	✓	Type 1
Not cost-effective	✓	✓	Type 2
Uncertain cost effectiveness	Uncertain	Uncertain	Type 3

Step 3: Identify points of agreement
Step 4: Systematically debate/clarify disagreements
Step 5: Weight criteria ('moderating factors')
Step 6: Define whose values and who decides?

The strengths of the approach

Employing the framework is likely to generate more questions than answers in its first application. However, the merit of the framework is in uncovering assumptions; transparently and systematically embedding a process that articulates values and priorities in anti-cancer drug funding decisions- decisions which are essential in both publicly funded and non-publicly funded systems. The Lipworth framework approach, much like accountability for reasonableness(9) which informs general UK prioritisation decision making, does not aim to have a single 'answer', which would be inappropriate to transfer across settings, but instead a systematic, transparent means to articulate a process. Critics of accountability for reasonableness (and the authors themselves) feel it aims to focus on fair process in decision making but is incomplete in how to quantify what is a substantive value or a 'relevant' criteria for prioritisation.(10, 11) Lipworth et al attempt to address both process and substantive questions in their work by outlining agreed principles and values, including

highlighting the need for harmonization of processes for Type 1 category drugs, as well as defining those areas which remain for debate.

Anti-cancer drugs compared with other cancer interventions

Although the advantage of the series of questions outlined in the Lipworth framework is the specificity to the anti-cancer drugs context, ultimately, for commissioners of services and policy decision makers, this also bears a risk. There will need to be some reconciliation in decision making to mitigate the risk of over-emphasizing anti-cancer drugs above other interventions which aim to improve cancer mortality and morbidity, such as interventions to improve early cancer diagnosis. Rather than an agreed aim of improved access to cancer drugs, the aim should be access to the most appropriate care for every patient. It is important not to lose sight of the fact that for some patients, the most appropriate treatment may not be anti-cancer therapy, but recognition of dying. Many high cost anti-cancer therapies are introduced in the incurable cancer setting and will not cure the cancer but aim to prolong life and improve quality of life. As Lipworth et al write in their broad areas of agreement, there is a "need to be compassionate which, depending on the context, might be achieved through access to medicine, or through the provision of alternative forms of care". So how do we define what is medically futile when it comes to cancer drugs?

Fair prioritisation and medical futility in the face of uncertainty: who decides?

The right to hope and therefore the 'right to try' (US) or the Medical Innovation Bill (UK) sends a powerful message that those with 'nothing more to lose' should have access to experimental treatment. The counter argument is equally emotive. Where the balance of 'right to try' has tipped too far, the potential for harm to the individual is false hope, which may rob them of quality of life before death and the lost opportunity to make their peace. It may even shorten life expectancy. There is also the question of societal cost- the right to try, some would argue, adds to the evidence base around these medications and their potential for use to extend life or for use in other earlier disease contexts (as adjuvant/neoadjuvant treatment) and therefore they may justify their cost to society and the individual. On the other hand, the costs to society may be too high in absolute financial terms, when considering the opportunity cost of money diverted from evidence based therapies, as well as generating concern the promised evidence may not materialize due to real world bias, rather than real world data.(12, 13)

Clinically Meaningful

By making greater use of clinically meaningful benefit scales developed by the American Society of Clinical Oncology [ASCO Value Framework](14) and the European Society of Medical Oncology [Magnitude of Clinical Benefit Scale] (15) can we more fairly define false hope at a population level? Although Lipworth et al. do not comment on these clinically meaningful scales the scales have the potential to complement their framework approach by including a transparent, measured assessment of drug 'value' and then the framework may be applied to incorporate moderating factors to reflect societal values. This may, for instance, identify where the tipping point is in different health systems around the right to try a therapy, despite its uncertain value to the individual and its financial cost to the system.

Assumptions and generalizability

Although the Lipworth framework aims to provide flexibility across settings so that individual countries can decide on the importance of social justice (e.g. universal healthcare utilitarianism and prioritiarianism) or whether libertarianism is the priority, the model may

still make assumptions. For instance, the framework suggests that there is an *agreed* tenant that there is a "need to promote equity and address existing inequities by attempting to fund medicines for patients who are already disadvantaged because of their disease (e.g. those with rare cancers) or their financial situation." This assumption may not hold true for all health systems. Similarly, by virtue of the tool forcing decision makers to evaluate safety, efficacy and cost-effectiveness, the framework implies these are 'essential criteria' for drug decisions and therefore cost-effectiveness is embedded even for non-publicly funded health systems.

If there is an 'answer' in the anti-cancer drug decision making debate it lies in clarity of information sharing both at the individual and population level. Health professionals have a duty of non-maleficence and beneficence and treatments of uncertain benefit, also have uncertain harms and unintended consequences at a population level due to opportunity costs and distorted incentives. Balancing patient advocacy with stewardship of scarce resources, as the authors describe, is challenging, but exposing assumptions and finding areas of common ground will improve accountability and provide an opportunity to reflect societies values in our choices for cancer care. Outstanding questions in cancer drug decision making include how can we make clinical drug outcome uncertainty more measured, meaningful, fair and sustainable in order to support population decision making: the Lipworth framework is a useful tool in the armory.

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